

U.S.S.N. 09/848,664

Filed: May 3, 2001

REVISED PRELIMINARY AMENDMENT

Please replace the paragraph on page 6, lines 13-19, with the following paragraph.

The peptides of the invention that bind heparin with high affinity have a characteristic amino acid domain that will not elute from a heparin-affinity column at less than 140 mM NaCl.

B² While many potential peptides exist, the inventors have identified several peptide sequences in particular. These are exemplified in the amino acid sequences identified in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5. Many other peptides may be used apart from the specifically enumerated sequences here.

In the Claims

1. (Amended) A [matrix] drug delivery composition comprising:

a substrate [capable of providing attachment of a heparin-binding peptide];

a peptide comprising a [binding] domain that binds heparin or heparin-like compounds with high affinity,

wherein the peptide is covalently bound to the substrate so that the heparin binding domain is able to bind to heparin or heparin-like compounds;

heparin or a heparin-like polymer; and

a protein growth factor or a peptide fragment thereof having a domain that binds heparin with low affinity, wherein low affinity is defined as not binding with heparin at a NaCl concentration of between about 25 mM and 140 mM.

Please cancel claim 2.

3. (Amended) The [matrix] composition of claim 1 wherein the domain of the growth factor or peptide fragment thereof is further defined as comprising a length of about 8 to

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30 amino acid residues comprising at least 2 basic amino acid residues, a ratio of basic to acidic amino acid residues of at least 2, and a ratio of hydrophobic amino acid residues to basic amino acid residues of at least 0.67.

4. (Amended) The [matrix] composition of claim 3 wherein the basic amino acid [residue is] residues are K or R.

5. (Amended) The [matrix] composition of claim 3 wherein the acidic amino acid [residue is] residues are further defined as D or E.

6. (Amended) The [matrix] composition of claim 3 wherein the hydrophobic amino acid [residue is] residues are further defined as A, V, F, P, M, I, or L or C when C is involved in a disulfide bond.

7. (Amended) The [matrix] composition of claim 1 wherein the growth factor or peptide fragment thereof is selected from the group consisting of neurturin, persephin, IGF-1A, IGF-1 β , EGF, NGF β , NT-3, BDNF, NT-4, [TGF- β 2,] TGF- β 3, [or] and TGF- β 4.

Please cancel claims 8-19.

20. (Amended) The [matrix] composition of claim [1] 65 wherein the substrate comprises fibrin.

21. (Amended) The [matrix] composition of claim [1] 65 wherein the substrate comprises a synthetic polymer hydrogel.

Please cancel claims 22 and 23.

24. (Amended) The [matrix] composition of claim [1] 64 wherein the heparin or heparin-like polymer has a molecular weight between about 3,000 and 10,000,000 Daltons.

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25. (Amended) The [matrix] composition of claim [1] 64 wherein the heparin-like polymer is a polysaccharide having a molecular weight between about 3,000 and 10,000,000 Daltons, and having at least one negative charge per two saccharide rings and no more than one positive charge per ten saccharide rings.

26. (Amended) The [matrix] composition of claim [1] 64 wherein the heparin-like polymer is selected from the group consisting of dextran sulfate, chondroitin sulfate, heparin sulfate, fucan, alginate, [or] and a derivative thereof.

27. (Amended) The [matrix] composition of claim 1 wherein the molar ratio of heparin or heparin-like polymer to growth factor or peptide fragment thereof is at least one.

Please cancel claims 28-56.

57. (Amended) [A] The composition of claim 1 in a vascular graft [comprising a matrix capable of supporting cell adhesion, said matrix comprising

bound heparin or heparin-like polymer and a growth factor having a low binding affinity for heparin].

58. (Amended) [An] The composition of claim 1 in an article for treatment of dermal wounds [comprising a matrix capable of supporting cell adhesion, said matrix comprising bound heparin or heparin-like polymer and a growth factor having low binding affinity for heparin].

59. (Amended) The [article] composition of claim 58, wherein the growth factor is TGF- β 3.

Please cancel claim 60.

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61. (Amended) [An] The composition of claim 1 in an implantable sterilized composition [comprising

a matrix capable of supporting cell adhesion, said matrix comprising bound heparin or a heparin-like polymer and a growth factor or peptide fragment thereof having low binding affinity for heparin].

62. (Amended) A method for providing controlled release of a growth factor comprising:

preparing a [matrix comprising a growth factor having a domain with a low affinity for binding heparin and bound heparin or heparin-like polymer] composition comprising

a substrate,

a peptide comprising a domain that binds heparin or heparin-like compounds,

wherein the peptide is covalently bound to the substrate so that the heparin binding domain is able to bind to heparin or heparin-like compounds,

heparin or a heparin-like polymer, and

a growth factor or a peptide fragment thereof having a domain with low affinity for binding heparin and bound heparin or heparin-like polymer, wherein low affinity is defined as not binding with heparin at a NaCl concentration of between about 25 mM and 140 mM; and

placing the composition on a wound in need thereof.